Ultrastructure in Glomerulonephritis Associated With Cryoglobulinemia

A Report of Six Cases and Review of the Literature

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Renal tissue from 6 patients with glomerulonephritis associated with cryoglobulinemia was studied by light microscopy, immunofluorescence microscopy, and electron microscopy. Fibrillar deposits in glomerular capillaries were observed in electron micrographs in 4 of 6 patients. The ultrastructure of these deposits is compared with those in 6 previously reported cases, with the ultrastructure of the serum cryoprecipitates, and with fibrillar glomerular deposits in other glomerulonephritides. It is concluded that serum cryoprecipitates are structurally similar to glomerular deposits and that these fibrillar deposits are a frequent and possibly distinguishing morphologic feature of glomerulonephritis associated with cryoglobulinemia. (Am J Pathol 88:145–162, 1977)

CRYOGLOBULINS OCCUR in the sera of patients with lymphoproliferative disorders, autoimmune diseases, and infectious processes, accounting for approximately 70% of cases of cryoglobulinemia.[1] Primary (idiopathic or essential) cryoglobulinemia accounts for the remaining approximately 30% of cases.[1]

In these patients, 21% have symptoms of renal involvement.[1] The presence of glomerulonephritis has been documented clinically and pathologically in both primary and secondary forms.[1,2] Cryoglobulinemia occurs in the setting of systemic diseases of which glomerulonephritis is a major component, e.g., systemic lupus erythematosus (SLE)[3-5] and polyarteritis nodosa[1] and also occurs in glomerulonephritis in the absence of systemic disease.[2,4,6,7] Also, cryoglobulinemia has been associated with glomerulonephritis in patients with chronic liver disease where the relationship between the glomerular and hepatic lesions is less clear.[4,8,9]

The histologic findings in the kidneys in cases of cryoglobulinemia and glomerulonephritis have been described in several reports.[1,4,6-19] Excluding cases of SLE and poststreptococcal glomerulonephritis (PSGN), about two-thirds of reported cases have been characterized by diffuse endocapillary proliferation. Slightly less than half of these have shown

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accentuation of the lobular architecture, increased mesangial matrix, and double contoured peripheral basement membranes. The remaining one-third of cases have shown a variety of histologic patterns, including membranous glomerulonephritis, focal glomerulonephritis, capillary basement membrane deposits without proliferation, and sclerosis. Thus glomerular changes at the light microscopic level are not specific. An additional histologic feature reported in some cases is the presence of eosinophilic hyaline thrombi in glomerular capillaries.

Immunofluorescence studies have,[1,4,8,10,11,13,17,18] with few exceptions,[12,14] demonstrated a correlation between granular glomerular deposits of immunoglobulin and serum cryoglobulins in that the class(es) of immunoglobulin in the cryoprecipitate have been represented in the glomeruli, and disappearance of the cryoglobulin from the serum has been associated with resolution of the glomerular lesion.[2,6] Electron microscopic studies have been reported in 11 patients.[10-19] In 6 of these,[11,12,16,18,19] deposits with a fibrillar structure in glomeruli have been demonstrated.

The purpose of this report is to present the pathologic features, in particular the ultrastructure of deposits in kidneys of 6 patients having glomerulonephritis associated with cryoglobulinemia. In 4 of these, deposits in glomeruli and, in 2, the serum cryoprecipitate had a fibrillar structure. Based on our findings and those collected in the literature, it is concluded that deposits with these fibrillar configurations are frequent and may be a unique morphologic marker of glomerular disease associated with cryoglobulinemia.

Materials and Methods

Renal biopsies and kidney tissue obtained from autopsies were fixed in Zenker's solution, and paraffin sections cut at 2 to 3 μ were stained with hematoxylin and eosin (H&E), periodic acid–Schiff (PAS), periodic acid–silver methenamine (PASM) counter-stained with H&E, azancarmine, Congo red, and crystal violet stains. For immunofluorescence microscopy, frozen sections were made from a portion of each specimen and stained with fluorescein-labeled antisera (Behring Diagnostics, Meloy Laboratories) against immunoglobulins G, A, and M as well as C3 and fibrin/fibrinogen. For electron microscopy a portion of each specimen was fixed in 2.5% glutaraldehyde, postfixed in 1% osmic acid, dehydrated in graded alcohols, and embedded in Epon 812. Thin sections were stained with uranyl acetate and lead citrate. Grids were examined in a Zeiss EM9 electron microscope. Serum cryoprecipitates from 2 patients were separated at 4 C and the centrifuged pellets were fixed in 2.5% glutaraldehyde and processed for electron microscopy as described above.

Results

Of the 6 patients, 4 were female, and the age range was 44 to 70 years (Table 1). In 4 patients with mixed IgG–IgM cryoglobulins, there was no

Table 1—Summary of Clinical Features

	Patient					
	RD	LG	LA	EP	SF	MP
Age/sex	67/F	64/M	69/F	70/F	44/M	55/F
Associated disease	Multiple myeloma	Lymphocytic lymphoma	None	None	Former heroin addict	None
Cryoglobulin class	IgG	IgG	IgG-IgM	IgG-IgM	IgG-IgM	IgG-IgM
BUN (mg%)*	60	136	80	72	29	32
Serum creatinine (mg%)*	4.0	3.8	3.5	3.5	1.2	1.0
Urine protein (g/24 hrs)	3.1	(2+)†	1.24	1.2	(3+)†	4.0
Clinical course	Died; autopsy revealed severe systemic vasculitis	Died shortly after biopsy; no autopsy	Stable renal function during 4 years' follow-up	Died in renal failure 2 years after biopsy; autopsy showed systemic vasculitis	Stable renal function for 2 years	Lost to follow-up

BUN = blood urea nitrogen.
* Highest values recorded.
† Estimated by Urostix.

Table 2—Light Microscopic Findings in Kidneys

	Patient					
	RD	LG	LA	EP	SF	MP
Number of glomeruli	Autopsy	27	12	15 (+ Autopsy)*	11	20
Endocapillary proliferation	Mild	Moderate	Severe	Severe	Severe	Severe
Lobulation of glomerular tufts	−	+	+	+	+	+
Increased mesangial matrix	+ Fibrillar	+ Nodular	+ Nodular	+ Nodular	+ Fibrillar	+ Nodular
Double contoured peripheral basement membranes	+	+	+	+	+	+
Capillary thrombi	−	+	+	+ (Autopsy only)	−	−
Small renal artery and arteriolar thrombi	+†	−	+	+†	+	−

* Autopsy 2 years after biopsy.
† Associated with vasculitis; characterized by fibrinoid necrosis.

associated disease although 1 of them was a former heroin addict. In 2 patients, the cryoglobulin class was IgG and both had lymphoproliferative diseases (myeloma and lymphocytic lymphoma). Impaired renal function as measured by serum creatinine and blood urea nitrogen (BUN) levels was present in 4 of 6 patients, and proteinuria occurred in all. The clinical courses were varied: of 5 patients in whom follow-up information is available, 2 have shown stable renal function while 3 died within 2 years, renal failure being a major contributing cause of death in all. Systemic vasculitis was present in 2 patients who died.

Histologic features in the kidneys at the light microscopic level are summarized in Table 2. In all 6 patients, glomeruli showed diffuse proliferation that was mild in 1 and moderate to severe in 5. The frequently seen increased mesangial matrix, lobular accentuation of glomerular tufts, and split or double contoured appearance of peripheral basement membranes in glomeruli of these patients resembled those usually found in membranoproliferative glomerulonephritis. Hyaline thrombi were observed in glomerular capillaries in 3 patients. In 4 patients arterial thrombi were observed. Two of these had associated vasculitis characterized as fibrinoid necrosis. Both died, and at autopsy systemic vasculitis, predominantly involving kidney, pancreas, and heart, were seen. Hyaline capillary thrombi were PAS positive in 1 of 3 patients (EP) and none stained for amyloid.

By immunofluorescence microscopy (Table 3), granular deposits of immunoglobulins were demonstrated in glomeruli in all 6 patients. In 1

Table 3—Immunofluorescence and Ultrastructural Localization of Deposits in Glomeruli

	Patient and serum cryoglobulin class					
	RD/ IgG	LG/ IgG	LA/ IgG-IgM	EP/ IgG-IgM	SF/ IgG-IgM	MP/ IgG-IgM
Immunofluorescence (antiserum)						
IgG	+*	+	−	+	+	+
IgM	−	+	+	+	+	+
IgA	±	−	−	+	±	−
C3	+	+	+	+	+	−
Fibrinogen	±	±	±	±	±	±
Ultrastructure (deposits)						
Intraluminal	−	+	+	+ (Autopsy only)	−	−
Mesangial	−	+	−	+	+	−
Subendothelial	+	+	+	+	+	+
Intramembranous	+	−	−	+ (Autopsy only)	+	+
Subepithelial	−	+	−	−	−	−
Cytoplasmic inclusions	−	+	−	−	−	−

± = presence in occasional sites in small amounts.
* Granular deposits were also present in renal arteries and arterioles.

patient (RD), similar granular deposits were observed in renal arteries and arterioles; some of these appeared normal by light microscopy while others showed fibrinoid necrosis. C3 was frequently present while fibrin was less constant and only in occasional sites. The class(es) of immunoglobulin which comprised the serum cryoglobulins generally were demonstrated in glomerular walls and in thrombi, when present in frozen sections. In the single exception, a patient with mixed cryoglobulinemia (LA), only IgM was demonstrated in a granular pattern along the peripheral basement membrane. This may have represented blocking of IgG by IgM as demonstrated in a similar case.[13]

The ultrastructural sites of localization of deposits in glomeruli are shown in Table 3. Subendothelial deposits were a constant finding. Other deposits were intramembranous in 4, intraluminal in 3, mesangial in 3, subepithelial in 1, and intracytoplasmic in 1.

With one exception (MP), deposits in glomeruli or the serum cryoprecipitate had a fibrillar character. The ultrastructural details in these 5 patients and in those of 6 patients previously reported are summarized in Table 4.

In 3 patients with mixed IgG–IgM cryoglobulins presented here (LA, EP, and SF), glomerular deposits appeared similar and consisted of curved cylinders and annular structures with spokes. As seen in the micrographs

Table 4—Ultrastructural Details of Fibrillar Deposits in Glomeruli and of Serum Cryoprecipitates in 5 Cases From the Present Study and 6 From the Literature

Patient	Immunoglobulin class(es) in serum cryoglobulin	Glomerular deposits	Serum cryoprecipitate	Reference
(1) RD	IgG	Irregularly electron dense, no distinct periodicity	Fibrillar	Present study
(2) LG	IgG	Straight bundles comprised of numerous fine fibrils; crosshatched.	NE	Present study
(3) LA	IgG-IgM	Curved cylindrical and annular	Cylindrical & annular	Present study
(4) EP	IgG-IgM	Curved cylindrical and annular	NE	Present study
(5) SF	IgG-IgM	Curved cylindrical and annular	NE	Present study
(6)	IgG λ paraprotein ?cryoprotein class	Fascicles comprised of fine fibrils and tubules, the walls of which are comprised of about 15 halos	NE	Schuurmans Stekhoven and van Haelst (1971)[16]
(7)	IgG	Fibers comprised of numerous fine fibrils	NE	Verroust *et al.* (1971)[18]
(8)	IgG	Fibers comprised of numerous fine fibrils; cross-striations	Fibrillar	Bengtsson *et al.* (1975)[11]
(9)	IgG-IgM	Described as identical with Patient 7, not illustrated	NE	Verroust *et al.* (1971)[18]
(10)	IgG-IgM	Cylindrical and annular structures	Cylindrical & annular	Cordonnier *et al.* (1975)[12]
(11)	IgG-IgM	Tubular and fibrillar	NE	Monga *et al.* (1976)[19]

NE = not examined.

(Figures 5 and 6), the cylinders are paired. Each measures 250 Å in width and is separated by a space 130 Å wide. Thus a bundle composed of two cylinders separated by a lucent area is 630 Å wide. Spoked annular structures are 300 Å in diameter, approximately the width of a single cylinder, suggesting that these represent cylinders in cross section. The frequent occurrence of annular structures in pairs supports this view. Cylindrical structures show transverse striations. Annular structures have electron-lucent centers around which are between eight to twelve projecting spokes. In optimally oriented cylinders a similar central lucent zone can be seen. As best estimated from published micrographs these configurations appear similar to those found in glomeruli in 2 patients previously reported (Table 4, Patients 10 and 11). In 1 patient (LA) the structure of the serum cryoprecipitate (Figure 11) and glomerular deposits (Figures 5 and 6) were similar as was true in a patient previously reported (Table 4, Patient 10). As seen in the micrograph (Figure 11) the cryoprecipitate was fibrillar with curved cylindrical and annular configurations. Cylinders were not clearly paired as in the glomerular deposits. They occurred in ill-defined groups. Spoked annular structures occurred singly or in groups. These measured approximately 250 Å in diameter.

The glomerular deposits are fibrillar also in patients with IgG cryoglobulinemia, but they differ in their structural arrangements from those in mixed IgG-IgM cryoglobulinemia. Whereas glomerular deposits in mixed cryoglobulinemia are made up of curved cylinders, those in IgG cryoglobulinemia in at least 2 patients (LG, and Patient 8, Table 4) were straight and aggregated in bundles. As seen in Figures 7 and 8, straight fibrils are aggregated into bundles measuring 800 Å wide and up to 1 μ long, depending on the plane of section. Nine to twelve fibrils make up each bundle. In cross-section bundles appear cross-hatched. Cytoplasmic inclusions in glomerular endothelial cells appear similar (Figure 9). In the second patient presented here (RD), the state of preservation of renal structures in autopsy tissue was inadequate and all that can be said is that glomerular deposits were nonhomogeneous. The cryoprecipitate in this patient, however, was ultrastructurally fibrillar (Figure 10) though not apparently aggregated into bundles as found in a patient previously described (Patient 8, Table 4). An additional IgG cryoprecipitate examined ultrastructurally [20] consisted of straight, parallel hollow tubules.

Discussion

Glomerular immunoglobulin deposits characterized ultrastructurally as fibrillar have been found in more than half of patients with cryoglobulinemia and glomerulonephritis examined by electron microscopy. This includes 4 of 6 patients from the present study and 6 of 11 patients

reported in the literature.[11,12,16,18,19] The serum cryoprecipitates of 4 patients examined were also fibrillar, and in 3 these were similar structurally and immunochemically to the deposits in glomeruli (Table 4). These findings suggest that circulating serum cryoglobulins are deposited in glomeruli, causing glomerulonephritis in some patients. Why glomerular disease occurs in some but not all patients with cryoglobulinemia [1] is not known. The high incidence with which such fibrillar deposits are found in patients with glomerulonephritis associated with cryoglobulinemia suggests that they may represent unique morphologic markers of deposits containing cryoglobulins. This would require substantiation by additional examinations of kidneys at the electron microscopic level from more patients with cryoglobulinemia.

The exact nature of these organized fibrillar deposits is not clear. In 3 patients with IgG cryoglobulinemia (Table 4, Cases 2, 7, and 8), glomerular deposits were morphologically similar and were composed of numerous straight parallel fibrils aggregated into bundles. These differed in structure from those in 5 patients with mixed IgG–IgM cryoglobulinemia (Table 4, Cases 3, 4, 5, 10, and 11) all of whom had deposits composed of curved cylindrical and annular structures. In Patients 6 and 9 (Table 4), valid comparisons with our cases cannot be made. In the former, the cryoprotein class is not specified, and in the latter the morphology is not illustrated. The observation that structural patterns of deposits may be related to specific cryoglobulin type raises the possibility that ultrastructural configurations may reflect specific physicochemical cryoprecipitation properties of these immunoglobulins. This requires testing by immunochemical analyses.

On the other hand, there is some evidence that such structures may in some cases represent viral particles. By the technique of negative staining, tubular and annular units identical with hepatitis B antigen have been demonstrated in the serum cryoprecipitate of a patient with hepatitis and mixed IgG–IgM cryoglobulinemia.[21] However, since both techniques, i.e., negative staining preparations as well as sections of embedded pellets, have not been utilized simultaneously to examine the same cryoprecipitate, conclusions regarding similarity cannot be drawn at this time. To our knowledge, only spherical viral particles have been shown in tissue sections of hepatitis virus–infected liver [22,23] and in kidney tissue from patients with renal disease associated with viral hepatitis.[24]

Thus, further studies are required to establish the nature and significance of fibrillar structures in patients with both mixed IgG–IgM and IgG cryoglobulinemia. Immunoelectron microscopy and immunochemical analysis of cryoprecipitates and glomerular eluates may provide definitive information.

The question of whether or not the ultrastructural characteristics of the glomerular deposits and cryoprecipitates as described in these patients is specific for deposits containing either IgG or mixed IgG–IgM cryoglobulins may be asked. The answer is not certain. In our own experience of approximately 800 renal biopsies examined by electron microscopy these configurations are unique to this group and none have been seen in other types of glomerular diseases. It is recognized that deposits of fibrillar type have been seen in glomerular disease of Henoch–Schönlein syndrome,[25] and that filaments forming so-called fingerprint patterns have been described in lupus glomerulonephritis [26] and in membranoproliferative glomerulonephritis; [27] however, these differ in structure from the ones described in the present patients. Whether the fibrillar deposits found in other such glomerular diseases may be related to the presence of unsuspected cryoglobulins seems remote but has not been specifically examined.

In 2 of our 6 patients presented here, deposits were without definite fibrillar structure, indicating that these ultrastructural characteristics are not necessarily a property of deposits in all cases of cryoglobulinemic glomerulonephritis. However, in one of these, renal tissue was available only from autopsy and was not optimally preserved. While the serum cryoprecipitate in this patient was fibrillar, it was not aggregated into bundles as in a patient previously described,[11] and as seen in glomerular deposits of our other patient with cryoglobulinemia of IgG type.

Glomerular capillary thrombi occurred in 3 of our patients and in each were ultrastructurally identical to deposits in other sites. In a recent review,[1] these were noted only in patients with cryoglobulins which contained monoclonal components. It is not known whether these thrombi occur *in vivo* and are functionally occlusive, or whether cryoprecipitation occurs *in vitro* prior to fixation. As judged by the size and frequency of distribution, thrombi were most striking in the 2 patients with the most clinically severe disease who died. Thus their presence in large numbers may bear some prognostic significance.

In addition to deposition in glomerular capillary walls, similar immunoglobulin deposition in renal and visceral arteries and arterioles was found by immunofluorescence in 1 of our patients with IgG cryoglobulinemia who died. Skin biopsies have also shown the presence of immunoglobulins identical to the cryoglobulin components within vessel walls in some cases.[28] Electron microscopic examinations have not systematically included vessels to search for fibrillar deposits within vessel walls.

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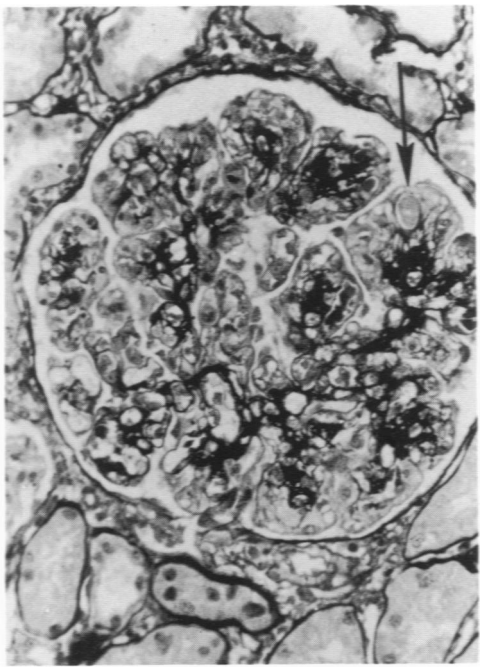
[*Illustrations follow*]



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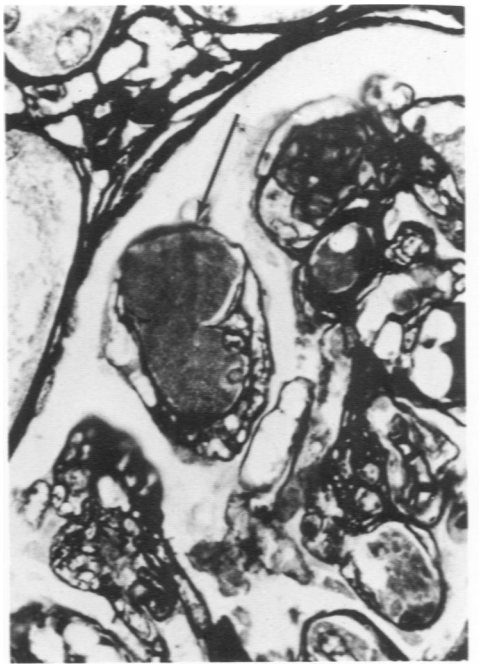

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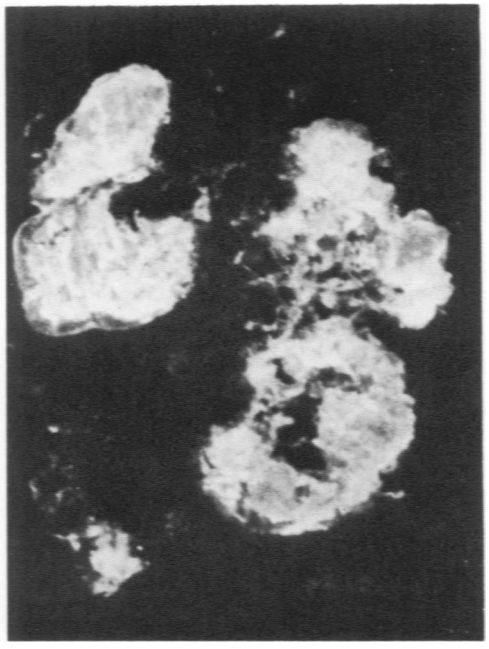

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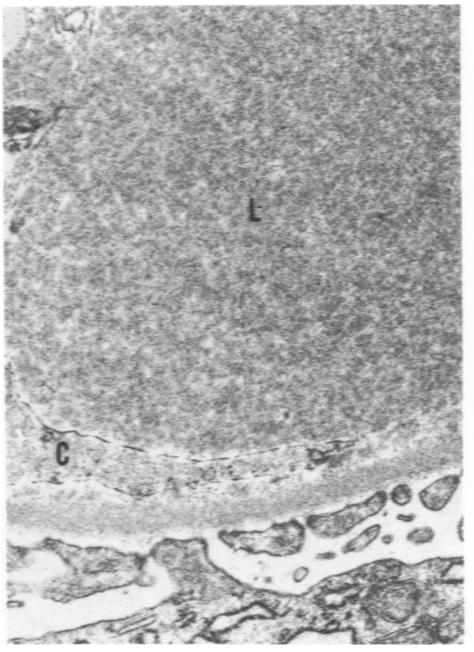

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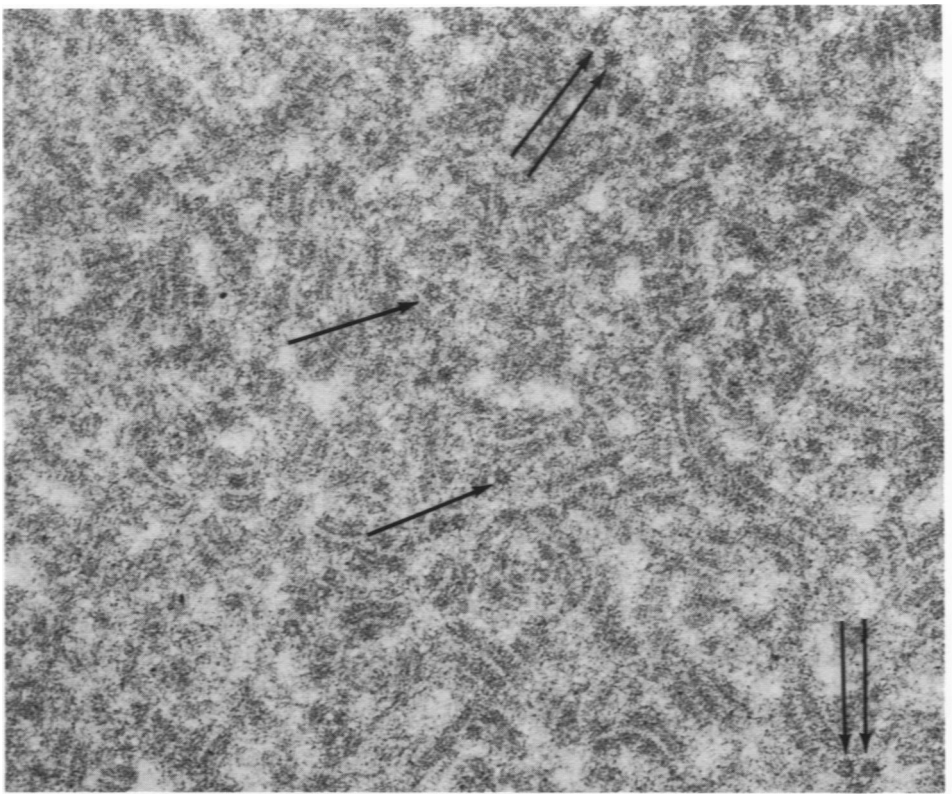
Figure 1—Patient LG with IgG cryoglobulinemia. Glomerulus with diffuse endocapillary proliferation, lobular accentuation, irregular dense accumulations of basement membrane like material in axial regions, and hyaline capillary thrombus (*arrow*). (PASM, × 350) **Figure 2**—Patient EP with IgG-IgM cryoglobulinemia. Portion of glomerulus showing peripheral capillary walls with double contoured basement membranes and hyaline thrombus in capillary lumen (*arrow*). (PASM, × 700) **Figure 3**—Patient LG with IgG cryoglobulinemia. Glomerulus stained with fluorescein-conjugated antihuman IgG showing staining of capillary walls and of capillary thrombi. (× 350) **Figure 4**—Patient EP with IgG-IgM cryoglobulinemia. Electron micrographs of a thrombus in glomerular capillary lumen (*L*), separated from the basement membrane by endothelial cell cytoplasm (*C*) (*lower left*) and in contact with basement membrane (*lower right*). These fibrillar deposits are similar to those in patient LA (Figures 5 and 6). (× 27,840)

Figure 5—Patient LA with IgG-IgM cryoglobulinemia. Electron micrograph of glomerular deposits composed of paired curved cylinders separated by an electron-lucent space. Spoked annular structures occur singly or in pairs (*arrows*). (× 68,320)

Figure 6—Patient LA with IgG-IgM cryoglobulinemia. Detail of fibrillar deposits. Curved cylinders with central electron-lucent zones (*short arrows*) and paired annular structures (*long arrows*) are seen. (× 133,120).



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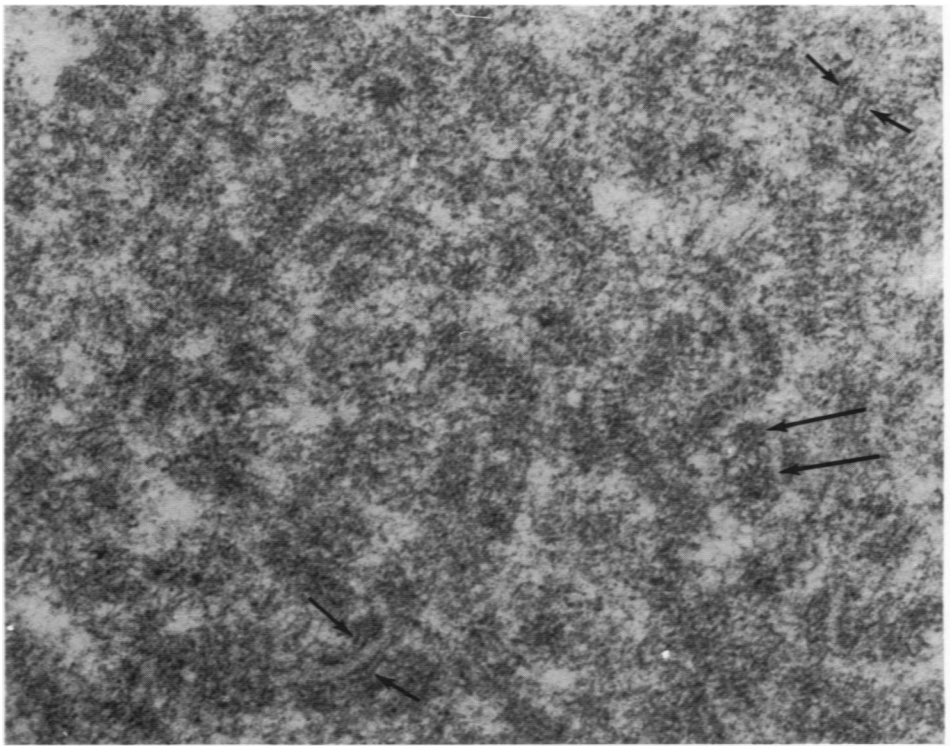

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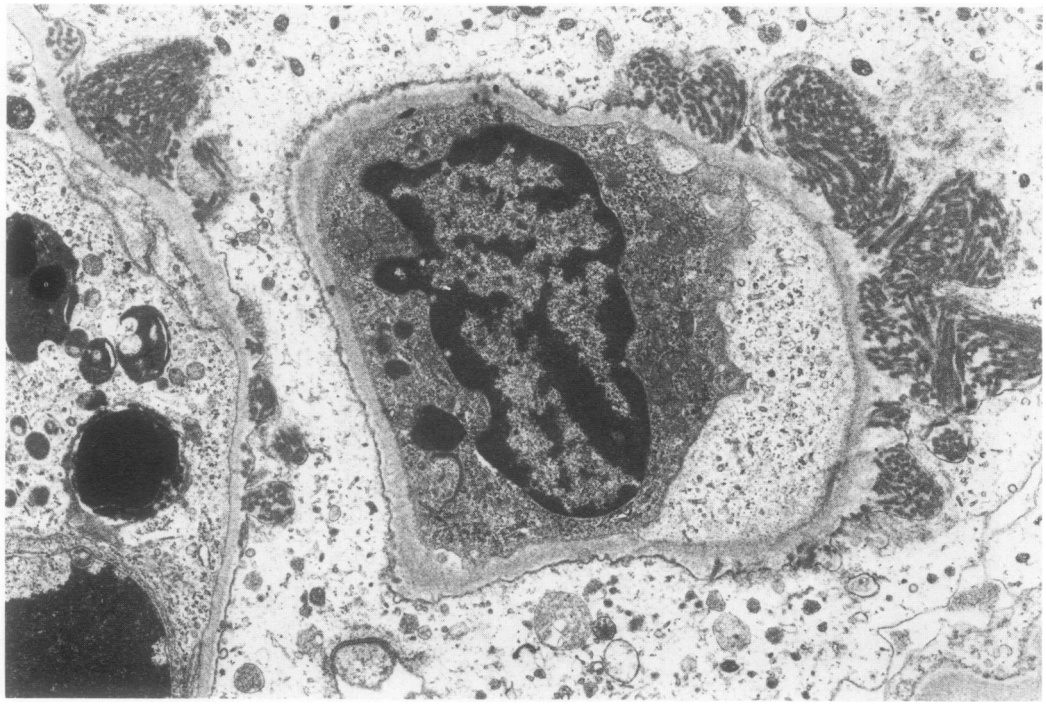

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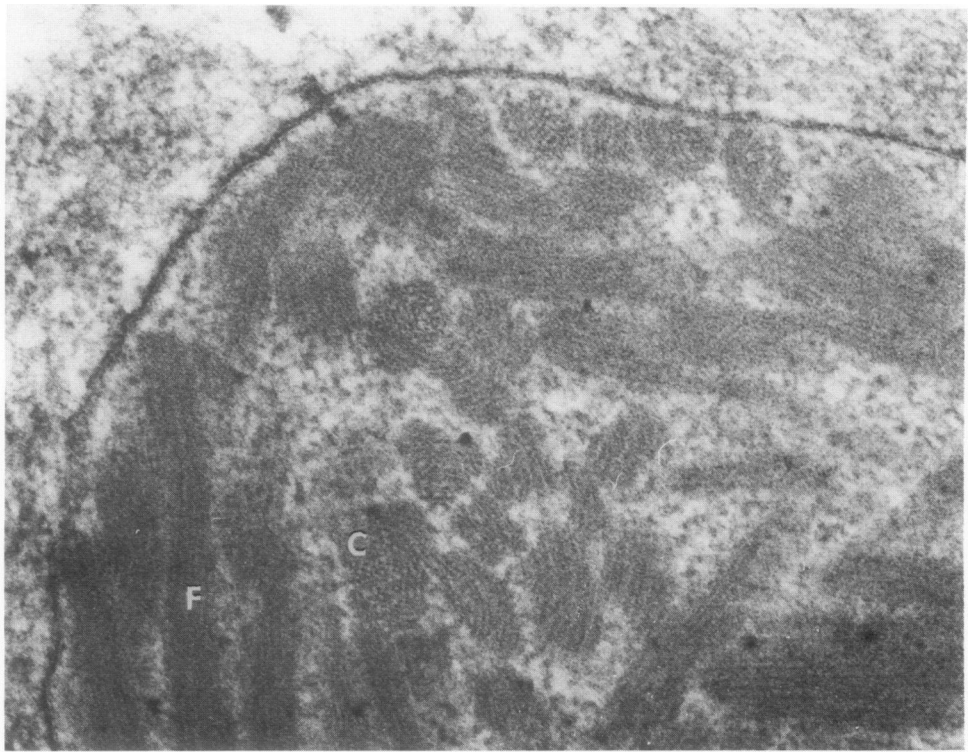

Figure 7—Patient LG with IgG cryoglobulinemia. Electron micrograph of peripheral capillary walls of two glomerular tufts showing subepithelial deposits composed of aggregated bundles, delimited by the plasma membrane of an epithelial cell. (× 5280) **Figure 8**—Patient LG with IgG cryoglobulinemia. Electron micrograph showing subepithelial deposits composed of bundles of parallel fibrils (*F*). In cross section (*C*), a cross-hatched configuration is seen. (× 68,320)

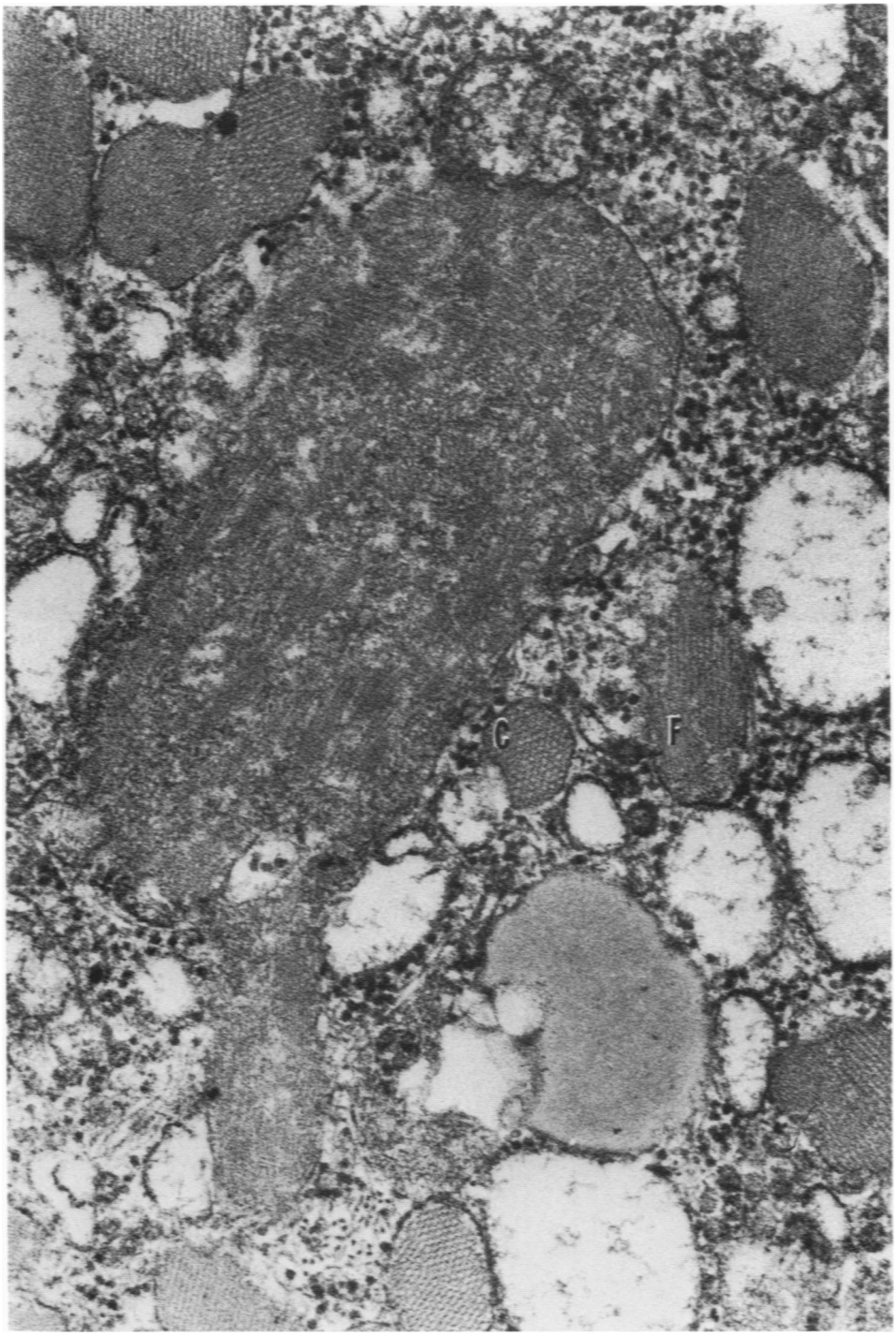

Figure 9—Patient LG with IgG cryoglobulinemia. Membrane-bounded intracytoplasmic inclusions in glomerular endothelial cells showing similar parallel fibrillar (*F*) and cross-hatched (*C*) arrays. (× 68,320)

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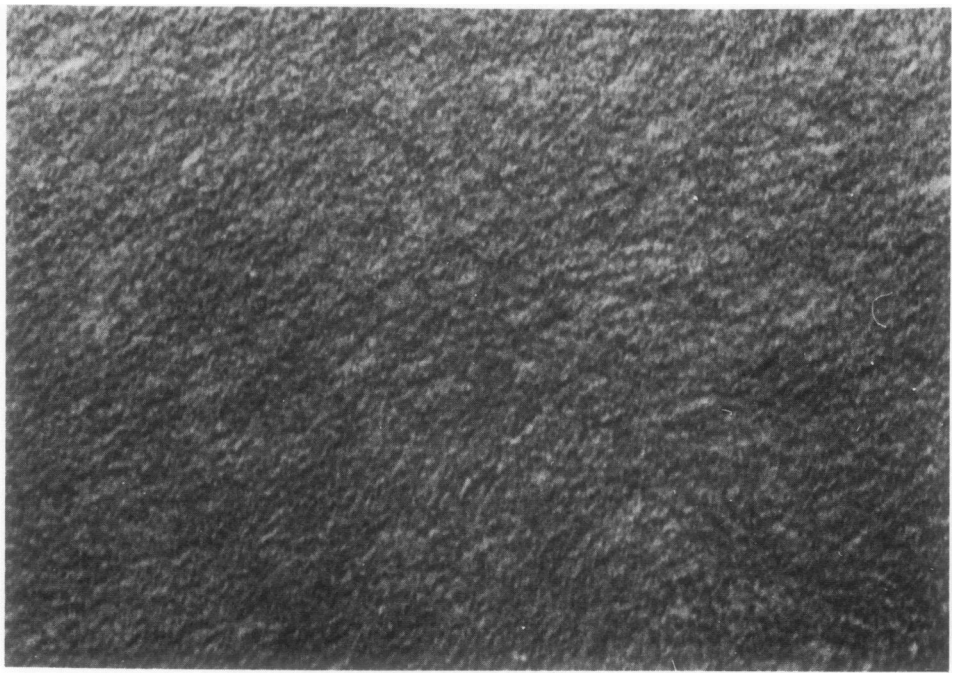

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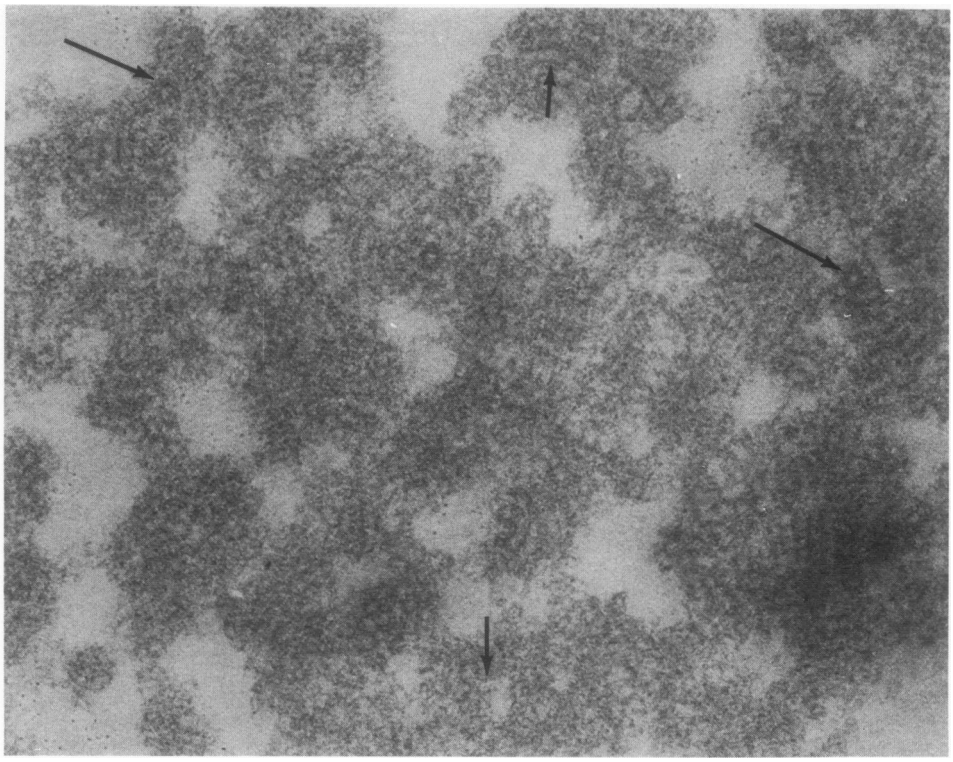

Figure 10—Patient RD. Electron micrograph of a pellet prepared from IgG serum cryoprecipitate (Cryopellet) (× 68,320). **Figure 11**—Paitent LA. Electron micrograph of IgG-IgM serum cryoprecipitate showing curved cylindrical (*short arrows*) and annular (*long arrows*) configurations. These bear resemblance to the glomerular deposits shown in Figures 5 and 6 from the same patient. (× 105,600)